Am. J. Trop. Med. Hyg., 89(4), 2013, pp. 781–783
doi:10.4269/ajtmh.13-0167

Short Report: Co-Morbid Infections in Hansen's Disease Patients in the United States: Considerations for Treatment

Madeline Bilodeau, Stephanie Burns, John Gawoski, Samuel Moschella, and Winnie Ooi*
Department of Infectious Diseases, Department of Dermatology, and Department of Laboratory Medicine, Lahey Clinic Medical Center, Burlington, Massachusetts

Abstract. 120 patients attending a Hansen's disease public health satellite clinic were evaluated for selected latent co-morbidities, consisting of strongyloidiasis, Chagas disease, hepatitis B, HIV, and tuberculosis, and potential exacerbation by immunosuppressive therapy. Implications for treatment of Hansen's disease are discussed.

Leprosy (Hansen's disease) is rare in the United States; there are approximately 6,500 reported current patients, roughly half of whom require active medical management. On average, 150 new cases are diagnosed annually. Approximately 90% of these cases are diagnosed in immigrants from developing countries where other chronic infections are endemic. In the United States, Hansen's disease is most frequently diagnosed by dermatologists, who may be unaware of, or uncomfortable with, treating these diseases. The current guidelines used by practitioners for public health satellite Hansen's disease clinics do not include routine screening for infections other than latent tuberculosis.

An under-appreciated challenge in Hansen's disease treatment involves reactivation of, or interaction with, asymptomatic infections caused by therapy given for Hansen's disease. These infections include chronic hepatitis B, chronic strongyloidiasis, latent tuberculosis, Chagas disease, and human immunodeficiency virus (HIV) infection. High-dose, moderate-term steroid therapy is frequently used to treat acute neuritis and type 1 or type 2 reactions in leprosy,[1,2] which are immunologically mediated inflammatory phenomena that may be seen before, during, or after multidrug therapy. Less commonly, tissue necrosis factor inhibitors, methotrexate, and cyclosporine may also be used to treat these inflammatory complications.[2] Type 2 reactions may also produce iritis, arthritis, neuritis, orchitis, and lymphadenitis, and often have protracted courses with episodes occurring over weeks, months, or years.

Seroprevalences of chronic hepatitis B, chronic strongyloidiasis, HIV infection, and Chagas disease were retrospectively evaluated in our study population during January 1, 2007–December 31, 2012. Screening serologic analyses were ordered routinely at the first visit to the Hansen's Clinic and not only when steroids were considered. However, Chagas antibody testing was added in April 2011, when it became readily available, for patients already in treatment at that time. Some of these patients may have been receiving steroid therapy when tested. HIV testing was limited to patients who gave informed consent. Hepatitis B surface antigen was screened by the AxSYM microparticle enzyme immunoassay (Abbott Laboratories, North Chicago, IL) for samples received before March 2010, and by the Advia Centaur chemiluminometric sandwich immunoassay (Siemens Healthcare Diagnostics, Tarrytown, NY) for samples received thereafter. Samples that were positive were referred to ARUP Laboratories (Salt Lake City, UT) for confirmation by antibody neutralization.

The HIV serologic analysis for HIV-1 and HIV-2 was performed using an AxSYM immunoassay analyzer (Abbott Laboratories) for samples received before December 2009, and using the Advia Centaur immunoassay until December 2011, after which HIV serologic analysis was performed using an Architect i1000 immunoassay (Abbott Laboratories). Confirmatory testing was not required because no samples failed HIV screening. *Strongyloides* and Chagas disease samples were assayed at the Centers for Disease Control (Atlanta, GA) using an enzyme immunoassay and indirect fluorescent antibody testing. We also screened for latent tuberculosis by using a 5 TU tuberculin skin test (purified protein derivative) and Centers for Disease Control and Prevention criteria for positivity.

One hundred twenty actively followed patients, consisting primarily of immigrants from Brazil, Southeast Asia, and Africa (Table 1), were treated at the Boston Hansen's disease clinic over the study period. The median age of the patient population was 50 years; 78% of the population was male. Six patients had tuberculoid leprosy, 27 had borderline tuberculoid leprosy, 43 had borderline lepromatous leprosy, 43 had lepromatous leprosy, and 1 had indeterminate disease. Of these patients, 80 (66.7%) were prescribed steroids and 2 were given tumor necrosis factor inhibitors over the course of their therapy; one received a brief course of cyclosporine. A total of 92.8% of patients who received steroids did so for six or more months. More than 50% of these patients were receiving steroids for more than two years. Of those who received steroids for six or more months, 14.8% were prescribed for patients with type 1 reactions and 85.2% for type 2 reactions.

Our findings are summarized in Table 2. In our population of 120 active Hansen's disease patients, a high percentage (66.7% overall) received steroids at least once during their therapy. A total of 75 of 120 patients were tested for chronic strongyloidiasis; 34 (45.3%) of 75 were positive. *Strongyloides stercoralis* is a common intestinal nematode that affects 30–100 million persons worldwide; it is endemic to Africa, Asia, Southeast Asia, and Central and South America. The fraction of patients who were positive for strongyloidiasis is consistent with the 46% reported for immigrant and refugee populations in the United States.[3] A total of 18 (52.9%) of 34 patients received steroid therapy. All who were positive were asymptomatic or had non-specific abdominal symptoms.

Total eosinophil count was not routinely checked, and fecal testing for ova and parasites was obtained for only

*Address correspondence to Winnie Ooi, Department of Infectious Diseases, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805. E-mail: winnie.w.ooi@lahey.org

TABLE 1
Regions of origin of study patients

Region of origin	No. patients
Africa	12
Asia and Micronesia	27
Central and South America, Caribbean	79
Europe	2

five patients who had *Strongyloides* larvae in feces. Serum *Strongyloides* titers are known to be more sensitive than fecal evaluation for ova and parasites for the diagnosis of chronic strongyloidiasis,[4] which is usually asymptomatic. Systemic steroid therapy is a well-known precipitant of disseminated strongyloidiasis to sites including lungs, liver, and central nervous system. One study estimated that dissemination occurs in 1.5–2.5% of all infected patients.[5] However, the reported prevalence of *Strongyloides* infection is difficult to assess, and is dependent upon geography, host immune status, and available diagnostic testing. A recent review of 213 case reports of severe or disseminated strongyloidiasis found steroid use to be the predisposing factor in 67%.[6] Glucocorticoid use causes acceleration of rhabditiform to filariform larval transformation in the gastrointestinal tract, resulting in an increased adult worm burden or hyperinfection in the human host. Even short courses (6–17 days) of corticosteroids have led to fatal hyperinfection.[7] Given the frequent need for steroid therapy during the treatment for Hansen's disease, all patients with a positive *Strongyloides* antibody titer were treated with ivermectin and followed-up until their titers became negative. Forty-five patients were not tested for strongyloidiasis, of whom 22 (48.9%) also received steroid therapy.

Eighty (66.7%) of 120 patients were screened for hepatitis B surface antigen. Nine (11.3%) of 80 were positive. American College of Immunization Practice guidelines recommend that all persons born in countries with greater than 2% endemicity for hepatitis B be screened for this infection.[8] Residual virus in a patient who previously had acute hepatitis B is controlled by cellular and humoral immune responses, but the virus can reemerge in the setting of immunosuppression. Acute hepatic necrosis may develop in these asymptomatic carriers or infected persons if given high doses of steroids.[9] One Hansen's disease patient with asymptomatic hepatitis B infection was treated with prednisone for erythema nodosum leprosum (an immune complex–mediated process) and fatal hepatic necrosis developed. Since that time, patients in our practice receiving steroids who have a significant hepatitis B viral load (4 of 8 of our remaining patients) have been given an antiviral regimen to avoid complications of reactivation.

TABLE 2
Patient testing results*

Testing result	No. tested of 120 (of 60 for Chagas disease)	No. (%) ever received steroids
Strongyloidiasis		
Positive	34	18 (52.9)
Negative	41	21 (51.2)
Not tested	45	22 (48.9)
Chagas disease		
Positive	0	0 (0)
Negative	18	14 (77.8)
Not tested	42	25 (59.5)
HBsAg		
Positive	9	5 (55.6)
Negative	71	38 (53.5)
Not tested	40	18 (45.0)
HIV		
Positive	0	0 (0)
Negative	52	30 (57.7)
Not tested	68	31 (45.6)
Tuberculosis		
Positive PPD	6	2 (66.7)
Negative PPD	33	17 (51.5)
Not tested†	81	42 (51.9)

*HBsAg = hepatitis B virus surface antigen: HIV = human immunodeficiency virus; PPD = purified protein derivative.
†Two not tested patients deferred the PPD test or did not show up for the reading. Both of these patients were receiving prednisone at some point during their treatment.

Despite the immune suppression seen in HIV-infected persons, an increased incidence of leprosy in HIV-positive patients has not been demonstrated. The HIV-positive patients with Hansen's disease who are treated with steroids may have increased susceptibility to opportunistic infections. Furthermore, immune suppression from prednisone also contributes to an increased HIV viral load and lower production of γ-interferon.[10] Erythema nodosum leprosum may be more frequent in HIV co-infected populations, and it is also suggested that HIV may worsen the risk for recurrent type 1 reactions, leading to poorer outcomes.[11] Since 2007, we have been screening all consenting patients for HIV antibody. A total of 52 patients (43.3%) of the total current population have been screened and all have shown negative results; two patients known to be positive for HIV infection were referred from other institutions and were receiving antiviral medications when seen in our clinic. Of our unscreened population, 45.6% have been receiving prednisone.

Chagas disease, which is caused by the protozoan *Trypanosoma cruzi*, is endemic to Central and South America.[12] Chagas disease, like Hansen's disease, is a chronic infection with different clinical manifestations that depend on the immune status of the patient. Chagas heart disease will develop in approximately 30% of patients with chronic infection, and is believed to be caused by the combined damage produced by the parasite and the host immune response. Chronic Chagas disease has been known to reactivate, often in the central nervous system of immunosuppressed hosts such as transplant patients, and when reactivation occurs may manifest with nonspecific symptoms.[13] Significant challenges in patient management have also been described in patients with erythema nodosum leprosum and unrecognized Chagas cardiomyopathy.[14] Since April 2011, efforts have been made to test our population, 51% (61 of 120) of whom are from endemic countries (Brazil and Colombia). To date, we have not identified any patient with chronic Chagas infection. Of the 42 at-risk patients not tested, more than half (59.5%) have been receiving steroid therapy, and none have shown evidence of reactivation.

The most common cause of active tuberculosis in the United States is reactivation of latent disease in foreign-born persons. Steroid therapy may reactivate latent tuberculosis. Of 39 patients tested, 6 (12.8%) had positive reactions to 5 TU tuberculin. Practical considerations prevent patients from returning for interpretation, leading to the low rate of known PPD status. However, daily rifampin, which is included in the therapeutic regimens for paucibacillary and multibacillary Hansen's disease in the United States, is effective prophylaxis for latent tuberculosis.

Infection with HIV, Chagas disease, hepatitis B infection, strongyloidiasis, and latent tuberculosis are co-infections that

need to be considered when treating immigrants with Hansen's disease in the United States. Frequent use of immunosuppressants, such as corticosteroids, may cause reactivation or exacerbation of potentially fatal dormant diseases. A significant number of our Hansen's disease patients were also infected with *S. stercoralis* and hepatitis B virus. It is unknown what percentage of patients with chronic strongyloidiasis will develop disseminated infection if given immunosuppressive doses of steroids. However, the case-fatality rate of disseminated infection approaches 86% in some studies. One of our patients, who had asymptomatic hepatitis B infection, died of acute hepatic necrosis when treated with high doses of steroids. Despite a large number of patients from Brazil, Chagas disease has not been detected in our population since April 2011, when we began screening at risk patients. Given the high risk for reactions and steroid use observed in our population, all patients being treated for Hansen's disease in the United States who come from areas endemic for strongyloidiasis, hepatitis B, tuberculosis, and Chagas disease should be screened for disease likely to be impacted by steroids and other immunosuppressive therapies. Screening should take place when the diagnosis is made and before multidrug therapy is initiated.

A limitation of this study is the absence of data correlating the length of steroid therapy with presence or absence of co-morbid infections. In addition, because all of our patients with known co-morbidities were treated or received prophylactic medications, we are unable to determine a risk ratio for patients who may remain untreated. Another limitation is the lack of screening results for all patients for each potential co-morbid condition. Nonetheless, our data suggest that these screening serologic analyses should be included for reimbursement in the satellite Hansen's disease program in the United States.

Received March 28, 2013. Accepted for publication July 15, 2013.

Published online August 26, 2013.

Authors' addresses: Madeline Bilodeau, and Winnie Ooi, Department of Infectious Diseases, Lahey Hospital & Medical Center, Burlington, MA, E-mails: bilodeau.ma@ husky.neu.edu, and winnie.w.ooi@lahey .org. Stephanie Burns and Samuel Moschella, Department of Dermatology, Lahey Hospital and Medical Center, Burlington, MA, E-mails: stephanie.a.burns@lahey.org and samuel.l.moschella@lahey .org. John Gawoski, Department of Laboratory Medicine, Lahey Hospital & Medical Center, Burlington, MA, E-mail: john.m.gawoski@ lahey.org.

REFERENCES

1. van Veen NH, Nicholls PG, Smith WC, Richardus JH, 2008. Corticosteroids for treating nerve damage in leprosy. A Cochrane review. *Lepr Rev 79:* 361–371.
2. Kahawita IP, Walker SL, Lockwood DN, 2008. Leprosy type 1 reactions and erythema nodosum leprosum. *An Bras Dermatol 83:* 75–82.
3. Posey DL, Blackburn BG, Weinberg M, Flagg EW, Ortega L, Wilson M, Secor WE, Sanders-Lewis K, Won K, Maguire JH, 2007. High prevalence and presumptive treatment of schistosomiasis and strongyloidiasis among African refugees. *Clin Infect Dis 45:* 1310–1315.
4. Pelletier LL Jr, Baker CB, Gam AA, Nutman TB, Neva FA, 1988. Diagnosis and evaluation of treatment of chronic strongyloidiasis in ex-prisoners of war. *J Infect Dis 157:* 573–576.
5. Milder JE, Walzer PD, Kilgore G, Rutherford I, Klein M, 1981. Clinical features of *Strongyloides stercoralis* infection in an endemic area of the United States. *Gastroenterology 80:* 1481–1488.
6. Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, Van Den Ende J, Bisoffi Z, 2013. Severe strongyloidiasis: a systematic review of case reports. *BMC Infect Dis 13:* 78.
7. Ghosh K, Ghosh K, 2007. *Strongyloides stercoralis* septicaemia following steroid therapy for eosinophilia: report of three cases. *Trans R Soc Trop Med Hyg 101:* 1163–1165.
8. Centers for Disease Control and Prevention, 1997. Immunization of Health-Care Workers: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep 46:* 1–42.
9. Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, Burra P, Caraceni P, Daniele B, Marco VD, Fabrizi F, Fagiuoli S, Grossi P, Lampertico P, Meliconi R, Mangia A, Puoti M, Raimondo G, Smedile A, 2007. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis 39:* 397–408.
10. Martel N, Cotte L, Trabaud M-A, Trepo C, Zoulim F, Gomes SA, Key A, 2012. Probable corticosteroid-induced reactivation of latent hepatitis B virus infection in an HIV-positive patient involving immune escape. *J Infect Dis 205:* 1757–1761.
11. Lockwood DNJ, Lambert SM, 2010. Leprosy and HIV, where are we at? *Lepr Rev 81:* 169–175.
12. Magill AJ, Reed SG, 2000. American Trypanosomiasis. Strickland GT, ed. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Eighth edition. Philadelphia, PA: W.B. Saunders Company, 653–664.
13. Walker M, Zunt JR, 2005. Parasitic central nervous system infections in immunocompromised hosts. *Clin Infect Dis 40:* 1005–1015.
14. Trindade MÃ, Carvalho NB, Belfort EC, Pagliari C, Gakiya E, Sakai-Valente NY, Benard G, Shikanai-Yasuda MA, 2011. A patient with erythema nodosum leprosum and Chagas cardiopathy: challenges in patient management and review of the literature. *Am J Trop Med Hyg 84:* 973–977.